REMARKS/ARGUMENTS

Claims 61–81 and 93–104 are pending and stand rejected in the instant application. Applicants have cancelled claims 68 and 69. Applicants have also amended claims 98 and 99. Support for these amendments can be found throughout the specification; no new matter is introduced.

Claim Rejections – 35 USC § 101

Claims 61–81 and 93–104 are again rejected under 35 USC § 101 for, in the Examiner's view, lacking utility. More specifically, the Examiner asserts that the claimed invention is not supported by a specific or substantial asserted utility or a well established utility. Applicants respectfully traverse this rejection for the reasons set forth below.

Applicants first reiterate that the utility requirement of § 101 is met either if the claimed subject matter has a "well-established" utility, or if a substantial, specific, and credible utility is disclosed in the specification.

> An invention has a well-established utility (1) if a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (*e.g.*, properties or applications of a product or process), and (2) the utility is specific, substantial, and credible.

Utility Examination Guidelines, 66 Fed. Reg. 1092, 1098 (Jan. 5, 2001). For example, "some uses can be immediately inferred from a recital of certain properties." *In re*

Folkers, 344 F.2d 970, 974 (C.C.P.A. 1965) (explicitly undisturbed by *Brenner* v. *Manson*, 383 U.S. 519, 535 n.23 (1966) and *In re Kirk*, 376 F.2d 936, 949 (C.C.P.A. 1967) (Rich, J., dissenting)).

The instant application relates to a nucleic acid microarray, comprising a plurality of nucleic acid probes addressably disposed upon a substrate, wherein each of said probes include genomic sequence of at least one predicted exon of a eukaryotic genome, at least 50% of said probes include genomic sequence of no more than one exon of said eukaryotic genome, said eukaryotic genome averaging at least one intron per gene, and wherein said plurality of nucleic acid probes averages at least 50 nt in length.

As summarized in the previous response, the nucleic acid microarrays of the instant application contains probes derived from genomic sequence of at least one predicted exon of a eukaryotic genome. The probes on the claimed microarrays are not from any random "fragments of genomic DNA from open reading frames of a eukaryotic genome". The probes are identified by various gene prediction programs and/or cross species comparative genomic sequence analysis. The claimed microarrays with these selected probes provide a valuable resource for high throughput gene discovery, the identification of alternatively spliced exons within a gene, the confirmation of predicted genes and exons, as well as providing expression verified single exon probes. Applicants respectfully submit that these are "well-established" utilities. In addition, Applicants

respectfully submit that specific, substantial utilities are disclosed in the instant application specification, and these utilities are credible.

Applicants respectfully submit that the claimed microarrays have a well-established utility. A brief review of the microarray field, including the various utilities, was given in the background section of the specification (page 6, line 19 through page 7, line 22). A search of the biomedical article collection (PubMed) of the National Library of Medicine identified 36 review articles published in English before January 31, 2000. Many of these review articles contain detailed discussion of the various utilities of microarrays.

Applicants hereby enclose, with the instant response, one of the review articles identified during this search, entitled "Microarrays: biotechnology's discovery platform for functions genomics", by Schena, M. et al., *Trends in Biotechnology*, 16(7): 301 – 306, 1998. In the review, Schena et al. gave a review of the state of the art of the microarray industry. They state: "Advances in microarray technology enable massive parallel mining of biological data, with biological chips providing hybridization-based expression monitoring, polymorphism detection and genotyping on a genomic scale. Microarrays containing sequences representative of all human genes may soon permit the expression analysis of the entire human genome in a single reaction. These 'genome chips' will provide unprecedented access to key areas of human health, including disease prognosis

and diagnosis, drug discovery, toxicology, aging, and mental illness. Microarray technology is rapidly becoming a central platform for functional genomics." (Abstract). They also compiles a list of key companies providing products and services for microarray research and development (Table 1), including such companies as Affymetrix, Genometrix, Hewlett-Packard, Nanogen, Synteni, as well as Amersham and Molecular Dynamics. The industry has since grown substantially larger and remains one of the top growth areas in the biotechnology industry.

There are also a great number of additional publications that comment on the general utility of the microarray platforms. Applicants include one of these articles with the instant response as well by R.W. Wallace entitled "DNA on a chip: serving up the genome for diagnostics and research" *Molecular Medicine Today*, 3(9):384-389, 1997. The Wallace reference also summarized the industrial applicability/utility of the microarray platforms (see Abstract and the entire article). Applicants respectfully submit that because cDNA and oligo-nucleotide microarrays have well-established utility, it is apparent to the artisan of an ordinary skill in the microarray field that the instantly claimed novel nucleic acid microarrays have well-established utility, as a platform for high throughput gene and exon discovery, for expression analysis of genes and alternative splicing analysis of exons, as well as for identifying gene and exon expression patterns. These are utilities that benefit greatly to the human health, including drug discovery, toxicity, disease prognosis and diagnosis. Applicants submit that these are

credible utilities and are not mere research tools that depend on further research to establish a use.

Applicants also wish to state again, hereinbelow, the substantial and specific utilities disclosed in the previous response. One of the utilities disclosed in the instant application for the claimed microarrays is high throughput gene discovery. Applicants "have used the methods and apparatus of the present invention to identify more than 15,000 exons in human genomic sequence whose expression we have confirmed in at least one human tissue or cell type. Fully two-thirds of the exons belong to genes that were not at the time of our discovery represented in existing public expression (EST, cDNA) databases, making the methods and apparatus of the present invention extremely powerful tools for novel gene discovery" (page 24 line 33 through page 25, line 8, also page 61, lines 24 – 32). "(T)he observation that 1/3 of the arrayed genes exist in expression databases provides powerful confirmation of the power of our methodology — which combines bioinformatic prediction with expression confirmation using genome-derived single exon microarrays — to identify novel genes from raw genomic data" (page 83, line 29, through page 84, line 2). An artisan of ordinary skill in the genomics art would immediately appreciate that the two-thirds of the exons mentioned hereinabove belong to novel genes not known by the public at the time. The microarray of the instant invention is thus a useful tool for high throughput gene discovery from any eukaryotic genome averaging at least one intron per gene.

Another utility disclosed in the instant application for the claimed microarray is the identification of alternatively spliced isoforms of genes among the large number of various cell types, developmental stages, and more importantly, physiologic conditions. The microarray of the instant application proves to be "exceedingly useful in the high throughput identification of a large variety of alternative splice events in eukaryotic cells and tissues" (page 25 lines 9 – 17 and page 29 lines 7 – 18). The utility of these microarrays in the identification of alternatively spliced isoforms of genes is "further described in commonly owned and co-pending U.S. patent application serial no. 09/632,366, filed August 3, 2000, the disclosure of which is incorporated herein by reference in its entirety" (page 29, lines 11 - 14). Here, all of the predicted exons of a gene are included on the microarray and in the subsequent expression analysis (see the specification, especially Figures 11 – 13 and Example 4 of the co-pending US patent application serial no. 09/632,366).

Another utility disclosed in the instant application for the claimed microarray is for verifying the expression of putative exons or genes predicted from genomic sequence (page 30, lines 18–26 and page 47, line 27 through page 48, line 9). These expression verified sequences are also useful as gene-specific probes (page 28, lines 30–31), and for gene discovery. Indeed, the utilities of the instant invention in gene discovery were

initially proven in the section entitled "Verification of Gene Expression" of the instant application (see page 83).

Because nucleic acid microarrays have well established utility, Applicants respectfully submit that the claimed nucleic acid microarrays are similarly useful. According to the Federal Circuit, "[t]he threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing **some identifiable benefit**." *Juicy Whip, Inc.* v. *Orange Bang, Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999) (emphasis added).

As stated hereinabove, the claimed inventions have well established utility. As stated in the previous office action and reiterated hereinabove, the specification described multiple specific, substantial, credible utilities for the claimed invention. Applicants respectfully submit that the claimed nucleic acid microarrays satisfy the utility requirements of 35 USC 101. Applicants also submit that the claimed microarrays satisfy the 35 USC 112, first paragraph. One skilled in the art at the time of filing knew how to make and use the claimed invention.

Claim Rejections – 35 USC § 112

Claims 68, 69, and 98–101 are rejected under 35 USC § 112, second paragraph as, in the Examiner's view, being indefinite for failing to particularly point out and distinctly claim the subject matter with which applicants regard as the invention. Applicants respectfully traverse these rejections.

Regarding claims 68 and 69, the Examiner states that the claims contain trademark/trade names and therefore does not comply with the requirement of 35 USC § 112, second paragraph. Solely to expedite prosecution, Applicants have cancelled claims 68 and 69, formally obviating the rejection. Applicants respectfully request that the rejection be withdrawn.

Regarding claims 98 and 99, the Examiner states that "the claims recite 'nucleic acid probes lack prokaryotic and bacteriophage vector sequence'." The Examiner requested clarification. In response, Applicants have amended the claims to change the language to "nucleic acid probes ... amplified from said eukaryotic genomic DNA". Applicants believe this new language is clear and unambiguous. Applicants respectfully submit that this language points out and distinctly claims the subject matter of the invention.

Claims 100 and 101 are rejected for the use of "homopolymeric stretches of A or T", because the Examiner believes it is unclear what constitutes a homopolymeric stretch. Applicants respectfully disagree. Applicants submit that "homopolymeric" is defined in the specification. Applicants direct the Examiner's attention to page 41, lines 6-8, of the specification, where a homopolymeric region is defined "as stretches of 25 or more, typically 30 or more, identical nucleotides."

In view of the above, Applicants respectfully request that the 35 USC § 112, second paragraph rejections of claims 68, 69 and 98–101 for being indefinite be withdrawn.

Applicants respectfully submit that the now pending claims 61–67, 70–81 and 93–104 are free of rejection. Applicants thus respectfully submit that the claims are in good and proper form for allowance and respectfully request the same.

If the Examiner believes that any issues remain outstanding, Applicants respectfully request that he call the undersigned for a further telephonic discussion.

Early and favorable action is earnestly solicited.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450, on February 9, 2005.

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